REMARKS/ARGUMENTS

Claims 1, 3, 4, 6-10 and 33-35 are active. Claims 2, 5, and 11-32 have been withdrawn from consideration. However, claim 5 has been amended to fall within the elected group and the Applicants respectfully request is rejoinder and examination. Claim 11 is listed as "withdrawn" since it relates to a lipophilic inner matrix. Minor edits have been made to claims 1, 6 and 35 in response to the Examiner's concerns or for clarity. Claim 1 has been revised to delete the term "derivative" and to specifically refer to peptides or proteins containing non-natural amino acids as described by page 7, lines 14-15 of the specification. With regard to claims 6 and 35, the definition of Eudragit® L appears on page 18, line 20 *ff.* of the specification and trademarked ingredients are generally defined by reference to their generic ingredients, MPEP 608.01(v). Nevertheless, this redundant term has been deleted from claim 35 which is directed to the elected species. The Applicants respectfully request that this after-final Amendment be entered by the Examiner to place this application in condition for allowance or at least in better condition for appeal. The proposed amendments do not raise new issues or necessitate a new search by the Examiner, since the amendment is based on elements earlier claimed or inherent in the previously examined claims, or amendments which simplify the claim language. Favorable consideration of this amendment and allowance of this application are respectfully requested.

Restriction/Lack of Unity/Election of Species

The Applicants previously elected with traverse **Group I**, claims 1-18 and 20-30, directed to an oral multiparticulate composition, and the species **centrorelix (active substance), anionic (meth)acrylate copolymers (e.g., EUDRAGIT® L type as the outer coating), absence of separating layer, and absence of biophilic matrix**. The requirement has been made FINAL. The Applicants understand that additional species will be rejoined

and examined upon an indication of allowability for a generic claim reading on the elected species. The Applicants respectfully request that the claims of the nonelected group which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04.

Provisional Rejection--Obviousness-type Double Patenting

Claims 1, 3, 4, and 6-11 were provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-5 and 17-19 of copending U.S. Application No. 12/030,377. This provisional rejection is traversed, since the active compound and the active substance (peptide or polypeptide) of the invention are different. The copending application and its claims relate to pellets with extraordinary high friability, see [0036-0038] of U.S. 2008/0206324A1. The abrasion resistance is markedly higher than in customary pharmaceutical forms instead of the standard test a modified test with much higher requirements was applied to determine their friability. The extraordinary high friability was achieved by forming the pellets by melt extrusion, die face cutting and subsequent rounding [0021]. A suitable extrusion temperature is for instance 160°C [0170], Example 1. Use of such a technique would denature and inactivate the active substance (peptide or polypeptide) of the invention. Thus, the claims of 12/030,377 do not cover the subject matter of the present invention which encompass an active substance that is a peptide or protein.

Moreover, the Applicants respectfully submit that the arguments herein remove all the remaining rejections. Accordingly, this provisional rejection may now be withdrawn since the claims in the copending application have not been allowed, MPEP 804(I)(B).

Rejection—35 U.S.C. §112, first paragraph

Claims 1, 3, 4, 6-9, and 11 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. Page 7, lines 6-17, of the specification describe both peptide- or protein- derivatives and conjugates. Nevertheless, claim 1 now has been revised to avoid this issue. Accordingly, this rejection may now be withdrawn.

Rejection—35 U.S.C. §112, first paragraph

Claim 33 was rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description on the grounds that the disclosure does not describe a composition that does not contain gelatin in its inner matrix layer. The Applicants traverse this rejection, since such a composition is exemplified in the specification (see the Examples starting on page 43 of the specification) and *ipsis verbis* or literal description of such a composition is not required. Under U.S. practice, a claim term need not be literally described in the specification.

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, **rather than the presence or absence of literal support** in the specification for the claim language (emphasis added)", In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1983).

In the present case, the disclosure clearly shows that the Applicants possessed the claimed subject matter (compositions containing an inner matrix not containing gelatin) since it is actually exemplified in the specification. Accordingly, this rejection may now be withdrawn.

Rejection—35 U.S.C. §112, first paragraph

Claim 34 was rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description on the grounds that the disclosure does not describe a composition "wherein said particles **do not have a layer separating the inner matrix and outer coating** . . .".

The Examiner asserts that particles without such a layer are not described by the specification. However, original claim 18, which indicates that "a separating layer is applied between the active substance-containing matrix layer and the outer film coating", shows that the Applicants possessed the concept of particles with or without such a separating layer. Also, the specification exemplifies particles that do not have a layer separating the inner matrix and outer coating (see the Examples starting on page 43 of the specification) and shows that the claimed subject matter was possessed by the Applicants as of their filing date, In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1983).

Moreover, the Examiner has required the Applicants to elect a composition which does not have such a separating layer (see page 3, section 3 and page 4 "Fourth Species Election Requirement" of the Lack of Unity/Restriction Requirement mailed February 1, 2008) Therefore, the Office has already taken the position that the elected species specifically described by claim 34 falls within the generic claim and is adequately disclosed. Therefore, for these reasons, this rejection cannot be sustained.

Rejection—35 U.S.C. §112, second paragraph

Claim 35 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This claim is directed to the elected species and this rejection is moot in view of the amendments above deleting the redundant term.

Mucoadhesive vs. Bioadhesive

To distinguish the invention from the prior art compositions it is important to recognize that the present invention stands for targeted release of a mucoadhesive active ingredient as opposed to agents that are bioadhesive and adhere to biological components other than mucous. Chitosan is one such mucoadhesive component and in the invention it is formulated to exert these mucoadhesive properties, that is, to specifically bind to the intestinal mucosa and release the active substance there (see the top of page 5 of the specification). As required by claim 1 the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there".

On the other hand, the prior art composition of Watts et al., U. S. Patent No 6,464,626, while containing chitosan, also contains a substantial amount of gelatin—a bioadhesive component that preferentially binds to glycocalyx on a cellular membrane instead of mucus. Claim 33 explicitly excludes gelatin and independent claim 1 requires release of the active substance when the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there". The Watts composition contains a high percentage of gelatin (see Examples 1-4 which incorporate 86.7%, 77.12%, 59.9% and 79.9% gelatin) and would exhibit bioadhesive effects which are disadvantageous compared to the mucoadhesive binding of the invention. The Watts compositions do not specifically target the active ingredient for mucosal release.

Since gelatin is the main component in the mixtures of Watts et al., the compositions of Watts et al. will bind in first place to the glycocalyx membrane. This type of binding is called "bioadhesive" in contrast to "mucoadhaesive". "Bioadhesive" means binding to the glycocalyx membrane but not to the mucus. This has the disadvantage that the particles are stuck or glued to glycocalyx of the intestine cells. This is undesirable because binding to the glycocalyx may cause irritation of the cells and unwanted pharmacological side effects.

Moreover, the addition of gelatin at least diminishes the beneficial effects of mucosal binding by chitosan and mucosal release of the active substance since the glycocalyx will be covered by gelatin complexes.

The present invention avoids these disadvantageous effects since mucosal-targeted complexes bound to the mucus can be washed away after the release of the active ingredient by the natural, on-going, renewal of the mucus layer. Further description of bioadhesive binding of gelatin to glycocalyx membrane is provided by WO 93/13753 at page 28, line 33-page 29, line 2 and at page 13, lines 14-23 and Fig. 3.

Rejection—35 U.S.C. §103(a)

Claims 1, 3, 6-8, 10, 11 and 34 were rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626. The Applicants refer to their prior arguments and address the Examiner's recent remarks below. The Applicants thank the Examiner for not imposing this rejection on claim 33, which expressly excludes an inner matrix layer containing gelatin.

The Examiner indicates that it is unclear what is excluded by the transitional phrase "consisting essentially of". As acknowledged in the OA, this term excludes ingredients, such as bioadhesive materials, that would affect the basic and novel characteristics of the inner matrix layer which are its "mucoadhesive effect" as expressly required by claim 1. The compositions exemplified by Watts contain 20% chitosan, but 80% bioadhesive gelatin. "Bioadhesive" refers to binding to the glycocalyx membrane, but not to the mucus. A bioadhesive composition has the disadvantage of sticking or gluing itself to the intestinal cells via the glycocalyx on their membranes. This causes irritation of the cells or other unwanted pharmacological side-effects. On the other hand, a composition which binds to the mucus, but not directly to the intestinal cells does not suffer from these disadvantages.

The significant amounts of gelatin found in the prior art compositions interfere with the mucoadhesive effect of the multiparticulate composition by adhering directly to intestinal cells and would thus affect the basic and novel characteristics required for the inner matrix layer. Therefore, significant amounts of gelatin (i.e., amounts that interfere with the mucoadhesive effect), such as those present in the prior art compositions, would be excluded by this transitional claim language.

The Examiner remains unclear about the difference between a "mucoadhesive" and "bioadhesive" compounds on the ground that both mucus and glycocalyx contain glycoproteins that have been assumed to bind to polymers similarly. However, the Office has provided no technical reasoning explaining why it believes different compounds equivalently bind to mucus and glycocalyx.

The residence time of mucoadhesives that bind to mucus or mucin differs from the residence time of bioadhesives that bind to cellular membranes. Mucoadhesives are removed by the natural turnover of mucus and thus have lower residence times than bioadhesive compounds like gelatin that bind to cells. Mucus/mucin provides a natural barrier to harmful components. For example, bacteria that are bound by mucus and which do not have bioadhesive properties (e.g., by cell binding proteins, pili, etc.) are washed off the mucosal surface. Similarly, the mucoadhesive properties of the invention limit the residence time of pharmaceutical agents and reduce toxicity and side-effects, while use of corresponding bioadhesive compounds like gelatin increase exposure time and side-effects. The bioadhesive properties of gelatin are described by Shaheen, et al., Int. J. Pharm. 2:504 http://www.ansijournals.com/ijp/2006/504-508.pdf (attached), see e.g., the Introduction which indicates that these bioadhesives bind to mucosal membrane. Accordingly, since the present invention is directed to mucoadhesive compounds, and the gelatin of the prior art compositions is a bioadhesive compound, this rejection may be withdrawn.

Rejection—35 U.S.C. §103(a)

Claims 1 and 4 were rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Berliner, et al., U.S. Patent No. 5,849,327.

Watts has been addressed above and does not disclose an inner matrix consisting essentially of a mucoadhesive polymer that targets release of the active component to the mucosa. Berliner was cited as a secondary reference teaching coating thickness, however, it also does not disclose or suggest the mucoadhesive inner matrix of the invention. Accordingly, this rejection may now also be withdrawn.

Rejection—35 U.S.C. §103(a)

Claims 1, 9 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Engel, et al., U.S. Patent No. 5,773,032. Watts has been addressed above and does not disclose an inner matrix consisting essentially of a mucoadhesive polymer that targets release of the active component to the mucosa. Engel was cited as a tertiary reference teaching the active ingredient centrorelix, however, it also does not disclose or suggest the other elements of the invention such as a mucoadhesive inner matrix. Moreover, none of the prior art suggests or provides a reasonable expectation of success that centrorelix would be compatible with the other components of the invention and be released as required by claim 1. Accordingly, this rejection may now also be withdrawn.

Rejection—35 U.S.C. §102

Claim 34 was rejected under 35 U.S.C. §102(b) as being anticipated by Shimono, et al., EP1203590. Claim 34, as it reads on the elected species, is not anticipated by Shimono since Shimono does not disclose centrorelix or an active peptidic substance embedded in the inner matrix layer. The compositions exemplified by Shimono contain acetaminophen a non-peptide drug and while the specification generically refers to a "medicament", this is insufficient to disclose the elected species under examination with sufficient specificity to anticipate the invention.

Shimono also uses chitosan only in combination with a water-insoluble polymer having a chitosan powder dispersed therein. Thus, after dissolution of the enteric coating this mixture will take a long time to dissolve. The chitosan will be released very slowly and thus will be spread over a large area of the intestine. This is quite different than the invention which provides immediate chitosan exposure which binds a specific target in a defined area of the mucosa.

Moreover, claim 34 indicates that there is no layer separating the inner matrix containing the cetrorelix and the outer coating. However, the water insoluble polymer layer (1, see abstract) of Shimono that contains chitosan particles separates the non-pareil layer (the "medicament-containing solid material", see abstract) containing the medicament/acetaminophen from the outer enteric polymer coating (2, see abstract). See also, Example 1 on page 11, top of col. 1 which shows that the chitosan layer separates the acetaminophen-containing layer from the enteric coating. Furthermore, the chitosan particles in the Shimono composition act as "pore forming" agent in the large intestine [0039] and not as a mucoadhesive component of an inner matrix layer as required by the present claims. Accordingly, this rejection cannot be sustained.

Rejection—35 U.S.C. §103

Claims 1 and 33 were rejected under 35 U.S.C. §103(a) as being unpatentable over Shimono, et al., EP1203590, in view of Watts, et al., U.S. Patent No. 6,465,626. As discussed above, neither Shimono nor Watts disclose all the elements of the elected species and, therefore, cannot render the claimed invention obvious. Shimono requires an insoluble polymer layer containing chitosan particles that separate the acetaminophen-containing non-pareil core from the enteric coating. Watts does not disclose an inner matrix consisting essentially of a mucoadhesive polymer that targets release of the active component to the mucosa. Accordingly, this rejection cannot be sustained.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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